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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/783,669	02/14/2001	D. Wade Walke	LEX-0135-USA	9659

24231 7590 01/05/2004

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EXAMINER	
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ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 01/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 121303

Application Number: 09/783,669
Filing Date: ***
Appellant(s): WALKE ET AL

Lance K. Ishimoto
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed October 10, 2003.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that the claims stand or fall together.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

Ji et al., 1998, J. Biol. Chem., Vol. 273, No. 28, pp. 17299-17302;

Yan et al., 2000, Science, 290, pp. 523-526 ;

Skolnick et al., 2000, Tibtech, Vol. 18, pp. 34-39;

Introduction to proteins and protein Engineering, 1986, Elsevier, p.41;

Bork et al., 1998, Current Opinion in structural Biology, Vol. 8, page 332-4.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 101

Claims 1-7 are rejected under 35 U.S.C. 101 because the claimed invention is drawn to an invention with no apparent or disclosed specific and substantial credible utility. The instant application has provided a description of an isolated DNA encoding a protein and the protein encoded thereby. The instant application does not disclose a specific biological role for this protein or its significance to a particular disease, disorder or physiological process, which one would wish to manipulate for a desired clinical effect.

It is clear from the instant application that the protein described therein is what is termed an "orphan protein" in the art. The DNA of the instant application has been isolated because of its similarity to a known DNA. There is little doubt that, after complete characterization, this DNA and encoded protein may be found to have a specific and substantial credible utility. This further characterization, however, is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which a novel

compound which was structurally analogous to other compounds which were known to possess anti-cancer activity was alleged to be potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" as it appears in 35 U.S.C. § 101, which requires that an invention must have either an immediate obvious or fully disclosed "real world" utility. The court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion".

The instant claims are drawn to a DNA and the protein encoded thereby of as yet undetermined function or biological significance. It is clear from the instant application that "The present invention relates to [...] novel human polynucleotides that encode membrane associated proteins and receptors" (page 1, lines 9-11 of the instant specification) designated novel human 7TM proteins NGPCRs. It is further described that "[e]xpression of the described NGPCRs can be detected in spinal cord, kidney, hypothalamus, and particularly in adrenal gland and heart kidney cells, among others" (page 2, lines 13-15). It is also asserted that "[t]he described NGPCRs are transmembrane proteins that fall within the 7TM family of receptors" (page 4, lines 13-14). However, in the absence of knowledge of the biological significance of this specific polynucleotide and encoded protein, there is no immediately obvious patentable use for the polynucleotide or the encoded protein. The similarity of the disclosed polynucleotide to polynucleotides encoding membrane receptor proteins does not make the instant polynucleotide

or encoded protein useful or significant as the known polynucleotides. According to the instant specification, NGPCR proteins can be used, for example, "as reagents in assays for screening for compounds that can be used as pharmaceutical reagents useful in the therapeutic treatment of mental, biological, or medical disorders (*i.e.*, heartbeat rate, etc.) and disease" (page 16, lines 26-31, emphasis added by the Examiner). However, the instant specification, as filed, fails to present any evidence of record, which would associate the instant DNA or encoded protein with any diseases or disorder.

Furthermore, it is known from the prior art that in spite of the fact that "a substantial degree of amino acid homology is found among members of [GPCR], but comparisons between subfamilies show significantly less or no similarity" (see Ji et al., page 17299, first paragraph and the whole paper). It is also general knowledge that amino acid structure cannot necessarily predict the function of the protein: "Knowing the protein structure by itself is insufficient to annotate a number of functional classes and is also insufficient for annotating the specific details of protein function" (see Skolnick et al., Box 2 on page 36). There are numerous publications available for review that indicate that even two-amino acid substitution in a molecular structure of a protein can lead to total loss of a protein to bind a specific receptor (see, for example, Yan et al., 2000). Thus, the structural homology of the proteins of the present invention to the proteins with a known function cannot *a priori* be predictive and conclusive of a function of the claimed proteins.

Therefore, to employ the nucleic acid molecules of the instant invention "in microarrays or other assay formats, to screen collections of genetic material from patients who have a particular medical condition" as asserted in the instant specification (page 10, second paragraph)

is not a real world utility because it would eventually relate to a protein for which no biological function is known. The instant application also fails to demonstrate use of the protein as a marker for any disease or condition (which would be a real world use). Because the instant specification does not teach a biological activity of the protein, one cannot prevent or treat a condition or disease as implied by the specification. To employ a polynucleotide of the instant invention in any of the disclosed methods would clearly be using it as the object of further research, which has been determined by the courts to be a utility, which, alone, does not support patentability. Since the instant specification does not disclose a credible "real world" use for the encoded protein then the claimed invention is incomplete and, therefore, does not meet the requirements of 35 U.S.C. § 101 as being useful.

Claim Rejections - 35 USC § 112

Claims 1-7 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a clear asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

(11) Response to Argument

Appellant traverses the rejection of claims 1 to 7 for lack of utility on premises that the described nucleic and amino acid sequences "encode variants of the human G protein-coupled receptor (MRGX2)" (bottom at page 3 going to page 4 of the Brief). Appellant submits that because the claimed nucleic acid sequence of SEQ ID NO: 4 is 100% identical to the sequence

deposited at GenBank and identified as MRGX2 receptor, than the "asserted utility for the described sequences is "credible" (page 4, third paragraph of the Brief). Appellant further argues that "it is well known to the art that novel human G-protein coupled receptors have a well-established utility" (bottom at page 4). This argument has been fully considered but is not deemed persuasive because it was never doubted or disputed by the Examiner that the instant claimed sequences most probably encode a G-protein coupled receptor based on the characteristic structural features of the instant polypeptide. However, the Examiner maintains the position that while the importance and significance of GPCRs generically as a class and as a target for pharmaceutical products is well known and well established, the patentable utility and biological significance of individual GPCRs such as the instant NGPCR, identified as "MRGX2" for the first time in the instant Brief, encoded by the claimed polynucleotides at the time of the invention remains unknown. The instant specification provided the disclosure of the structure of the claimed isolated nucleic acid molecules and of the polypeptide encoded thereby. It is clear that the protein encoded by the instant nucleic acid is structurally related to GPCRs. What is not clear and not disclosed is the biological significance of the instant receptor and, most importantly, its physiologically relevant ligand to control NGPCR activity. Without knowledge of the natural ligand of the newly discovered NGPCR encoded by the claimed nucleic acid molecules, one skilled in the art would not know what is the specific pathway that is regulated by this instant NGPCR, and, consequently, not be able to use the claimed polypeptide to regulate any physiological function. Moreover, the art clearly recognizes vast diversity of GPCR functions. It is also well-known fact that GPCRs do not share the same utility.

Appellant further asserts that a protein of the instant invention belongs to a family of proteins of which some members are the targets of over 60% of the therapeutic agents currently on the market (bottom at page 4 continuing on page 5). This number is actually higher since a number of agents such as antidepressants and hypertension medications were being employed clinically before their site of action was known. However, each clinical agent, which has been developed by measuring its interaction with a specific G protein-coupled receptor, was evaluated against a receptor whose native ligand and physiological function were known, such as the adrenergic receptors, the dopamine receptors and the serotonin receptors. There are also numerous G protein-coupled receptors, which do not mediate clinically significant process. More importantly, an artisan knew, before they employed a specific G protein-coupled receptor to identify clinically useful compounds, which physiological process or processes they wished to manipulate and that the protein employed in their assay had an influence of that process. Even if one identifies an agonist or antagonist for a receptor of the instant invention, this information is useless since one has no idea of what clinical effect the administration of that agonist or antagonist to an individual would have.

Appellant's arguments that the office has issued other GPCR patents (pages 5-6 of the Brief 10) are not persuasive. It is well settled that the prosecution of one patent application does not affect the prosecution of an unrelated application. *In re Wertheim*, 541 F.2d 257, 264, 191 USPQ 90, 97 (CCPA 1976) (holding that "[I]t is immaterial in *ex parte* prosecution whether the same or similar claims have been allowed to others"). Accordingly, Appellant's arguments with respect to the other issued U.S. Patents describing different GPCRs are unavailing.

Appellant submits that because the instant NGPCR ("MRGX2") "is expressed in sensory neurons that function to detect painful stimuli" then the claimed sequences have credible utility "for its biological role and as a drug target" (page 6, second and third paragraphs of the Brief). This argument has been carefully considered but is not persuasive for the reasons that follow. First, according to the instant specification, as filed, ""[e]xpression of the described NGPCRs can be detected in spinal cord, kidney, hypothalamus, and particularly in adrenal gland and heart kidney cells, among others" (page 2, lines 13-15). Thus, there appears to be no information presented in the instant specification that would indicate the specific pattern of distribution of the novel NGPCRs associated particularly with sensory and especially with nociceptive pathways. Second, even if to assume that the instant claimed NGPCRs were only expressed in sensory neurons, one would not know how to use the claimed sequences without knowledge of a specific biological function that is regulated by these NGPCRs, such function which one would wish to manipulate for a desired clinical effect. Based on the pattern of tissue distribution one skilled in the art would clearly not be able to make any credible conclusion regarding the physiological significance of the instant NGPCR and, therefore, would have to resort to substantial experimentation to discover the practical utility of the instant claimed sequences. However, 35 USC § 101 clearly states that the invention must be useful in currently available form, which precludes any further experimentation to establish the utility of the claimed invention.

Appellant's analysis of Example 10 of the Revised Interim Utility Guidelines Training Materials and comparison to the present application (bottom at page 6 continuing to page 7 of the Brief) has been carefully reviewed but is not deemed to be persuasive. In Example 10, a DNA which has a structural similarity to a DNA encoding a ligase, has been found to have a utility

because enzymes ligases have a well established utility in the art. However, this appears to be not the factual situation here. Each enzyme has a substrate specificity, which defines its unique biological function; therefore, an inhibitor of a specific enzyme obviously would have a specific and substantial credible utility. In the instant case, G-protein coupled receptors do not share a common utility but rather define a superfamily of receptors with a diverse range of biological activities (see earlier in the instant office action). The proper analysis of the instant claims, which are drawn to an isolated nucleic acid molecules encoding a polypeptide of yet undetermined significance, should be made in light of Example 12 of those guidelines, which explains why an isolated nucleic acid encoding an "orphan receptor" lacks utility in the absence of the disclosure of a specific role for either the nucleic acid or protein in a known disease or disorder or a physiological process which one would wish to manipulate for clinical effect. While not required by any statute or rule, if Appellants had disclosed a biological role or function of the claimed polypeptides, such might support a disclosed utility, such as for diagnosis or treatment of disease. However, no such role has been disclosed. This alone is not probative of lack of utility under 35 U.S.C. § 101, but is merely one of the analyses, which must be made. If there were another specific, substantial and credible utility disclosed for the claimed NGPCR, that would, in the absence of any knowledge of the biological function or role of the claimed polypeptides, be sufficient to establish utility.

Appellant further argues that reference of Ji et al. (incorrectly identified as Tae et al. in the previous office action), in fact, supports "that homology with members of a G-protein coupled receptor is indicative that the particular sequence is in fact a member of [particular subfamily of GPCR proteins]" (pages 7-8 of the Brief). Additionally, Appellant submits that

reference of Skolnick et al. admits that "sequence-based approaches to protein-function prediction have proved to be very useful", and that publication of Yan et al. cites only one example when two amino acid change in ligand structure lead to binding to two distinct receptors. Similarly, Appellant criticizes the art provided by the Examiner in the Final office action (pages 8-10). Appellant's arguments have not been found persuasive for the following reasons.

Appellant asserts the biological function of the claimed novel GPCRs based on structural similarities and homology to the known GPCR. As fully explained earlier, the Examiner maintains that there is no disagreement that the claimed nucleic acid sequences most probably encode a novel G protein-coupled receptor. The references quoted in the previous office actions all support the general idea that structural similarity does not necessarily lead to certain functional predictions. Persons skilled in the art know that changing one amino acid in a sequence gives, by definition, a new protein, and that according to the state of the art functional characteristics of a protein cannot be unequivocally extrapolated from its structural characteristics. This is even truer in view of the fact that the family of G protein-coupled receptors constitutes structurally related (seven transmembrane domain proteins) but functionally diverse proteins. Appellant's own statement that "G protein-coupled receptors are associated with a wide variety of cellular functions " (middle at page 11 of the Brief) only confirms that the instant NGPCR most probably will have a utility in drug development as soon as their specific role in a particular "cellular function" is discovered. Until then, Appellant's invention is incomplete and, therefore, clearly does not meet the requirements under 35 USC § 101 as being useful.

Beginning at the bottom of page 11 of the Brief, Appellant further argues that "the present sequences are specific markers of the human genome, and [...] would be an ideal novel candidate for assessing gene expression using [...] gene chips". The employment of the nucleic acids of the instant invention in a DNA chip is not a substantial or specific utility. Regarding the merit of the argument, any naturally occurring polynucleotide can be used in a DNA chip, and thus this asserted utility is not specific. The instant specification does not substantiate a link between the claimed polynucleotides and any specific disorder. The specification merely discloses that the claimed polynucleotides encode proteins that are structurally related to GPCR, and that they are expected to be involved in "mental, biological, or medical disorders (*i.e.*, heartbeat rate, etc.) and disease" (page 16, lines 26-31, emphasis added by the Examiner). The specification does not provide any evidence that the claimed polynucleotide is expressed at an altered level or form in any diseased *versus* healthy tissue. In the absence of any disclosed relationship between the claimed polynucleotide or the protein that is encoded thereby and any disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the polynucleotide itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson*, 148 USPQ at 696.

Appellant argues that specific utility of the claimed nucleic acids when used in a DNA chip is justified because of their "real world" substantial utility" (page 13, bottom of the page). This has not been found to be persuasive for the reasons fully explained earlier. Briefly, the disclosure that the instant NGPCRs are structurally related to GPCRs does render the asserted utility specific, since the specification does not establish that the instant NGPCR polypeptides

are expressed in any diseased tissues in any way that is different from the way they are expressed in healthy forms of the same tissues. In other words, the specification does not disclose that the NGPCR themselves are expressed in tissues associated with any disease at altered levels or forms. Thus, it is not a target for drug development, toxicology studies, or disease diagnosis. Significant further research would have to be conducted to identify diseases or disease states which correlate with altered levels or forms of the claimed polynucleotides. Therefore, this asserted utility is not applicable to the claimed invention in its currently available form.

Furthermore, to accept Appellant's argument that "the present nucleotide sequence has [the specific utility] in determining the genomic structure of the corresponding human chromosome" (page 15, last paragraph of the Brief) would be comparable to conceding that any object of fixed mass has *prima facie* utility as a weight standard, irrespective of any other properties possessed by that object. It was just such applications that the court appeared to be referring to when it expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation (*Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966)). Because the steroid compound, which was the subject of that decision had a known structure and molecular weight it could have readily been employed as a molecular standard at that time. Further, because that compound was a hydrocarbon it certainly could have been employed in the well-known process of combustion for purposes of lighting and/ or the generation of heat. The generation of heat by combustion of hydrocarbons certainly was and remains an important process. Irrespective of such obvious utilities, the court still held that the compound produced by the process at issue in *Brenner v. Manson* did not have a specific and substantial utility (emphasis added).

To grant Appellant a patent encompassing an isolated polynucleotide encoding a naturally occurring human protein, which is not readily usable in it's current form, would be to grant Applicant a monopoly "the metes and bounds" of which "are not capable of precise delineation". That monopoly "may engross a vast, unknown, and perhaps unknowable area" and "confer power to block off whole areas of scientific development, without compensating benefit to the public" *Brenner v. Manson, Ibid*). To grant Applicant a patent on the claimed polynucleotide based solely upon an assertion that it can be employed in a DNA chip is clearly prohibited by this judicial precedent since the compensation to the public is not commensurate with the monopoly granted and would be no different than granting a patent on the process disputed in *Brenner v. Manson* on the premise that the steroid produced thereby was useful as an analytical standard or as a fuel source.

Appellant further summarizes case law on the utility requirement and refers to *Juicy Whip v. Orange Bang* (Fed. Cir. 1999), which held that in order to violate the utility requirement, an invention must be "totally incapable of achieving a useful result", and to *Cross v. Iizuka* (Fed. Cir. 1985), which stated that "any utility of the claimed compounds is sufficient to satisfy 35 U.S.C. § 101" (page 17, first paragraph). The essential disagreement appears to be the interpretation of *In re Brana*, 51 F.3d 1560,1566, 34 USPQ2d 1436 ,1441 (Fed. Cir. 1995). That court decision determined that a compound which belonged to a family of compounds known to have anti-tumor activity, which is a common and well established specific and substantial utility for that family of compounds, would be reasonably expected to have anti-tumor activity in light of positive *in vitro* data with respect to that particular compound since that data has proven to be an indicator of anti-cancer activity by other members of that family. The protein, NGPCR or

"MRXG2", of the instant invention does not belong to a family of compounds with a common well-established specific and substantial utility. The utility of those members of the receptor family to which the claimed protein in the instant application belongs lies in the knowledge that they modulate a specific physiological activity in response to a specific ligand. Since the instant specification does not disclose the identity of a native ligand for the claimed protein, knowledge of the pathway through which that receptor transduces its signal in response to that ligand is not particularly useful. Moreover, the instant specification did not provide any *in vitro* data that would be accepted as predictive of *in vivo* results, and there is no description of the clinical administration of NGPCR of the instant invention. Therefore, the Examiner maintains the position that Appellant's reliance on *In re Brana* is misplaced.

Appellant's reliance on case law pertinent to 35 USC § 112, first paragraph (page 18, first paragraph), is also misplaced because the instant rejection is a utility and not an enablement rejection. 35 USC § 101 clearly states that the invention must be useful in currently available form, which precludes any further experimentation to establish the utility of the claimed invention. The fact that Appellant submits that some experimentation may be required to practice the claimed invention simply confirms that the instant invention was not completed as filed, and, therefore, clearly lacks utility in currently available form.

At page 16 Applicant submits "that the claimed polynucleotide sequences define how the encoded exons are actually splices together or produce an active transcript" and, further, that "the practical scientific value of expressed, spliced, and polyadenylated mRNA sequences is readily apparent to those skilled in the relevant biological and biochemical arts". The Examiner agrees that there is little doubt that after complete characterization the claimed nucleic acid and

encoded proteins may be found to have a specific and substantial credible utility. However, this characterization is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. To employ a polynucleotide of the instant invention as the object of further research has been determined by the courts to be a utility, which, alone, does not support patentability.

Finally, Appellant's argument regarding other U.S. patents issued to different G protein-coupled receptors (pages 18-19 of the Brief) was fully answered earlier in the instant office action. Briefly, the prosecution of one patent application does not affect the prosecution of an unrelated application. *In re Wertheim*, 541 F.2d 257, 264, 191 USPQ 90, 97 (CCPA 1976) (holding that "[I]t is immaterial in *ex parte* prosecution whether the same or similar claims have been allowed to others").

Because the claimed invention is not supported by either a clear asserted utility or a well established utility for the reasons set forth earlier, one skilled in the art clearly would not know how to use the claimed invention. Therefore, it is believed that the rejection under 35 U.S.C. § 112, first paragraph, should be sustained.

Therefore, for reasons set forth above, Appellants arguments have been fully and carefully considered, but are not considered sufficient to rebut the prima facie case of lack of utility and failure to enable due to lack of utility and it is believed that the rejections should be sustained.

Respectfully submitted,

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December 15, 2003

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